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Modelling weekly vector control against Dengue in the Guangdong Province of China

Biao Tang [a,c], Yanni Xiao [a,*], Sanyi Tang [b], Jianhong Wu [c]

[a] School of Mathematics and Statistics, Xi'an Jiaotong University, Xi'an 710049, PR China
[b] College of Mathematics and Information Science, Shaanxi Normal University, Xi'an 710062, PR China
[c] Centre for Disease Modelling, York Institute for Health Research, York University, Toronto, ON, Canada M3J 1P3

HIGHLIGHTS

- A mathematical model is formulated to study weekly vector control effect on dengue epidemic.
- Estimations of reproduction number verified the high effectiveness of the control programs.
- Choice of dates of initiating intervention and killing ratios is essential for cubing epidemic.
- Main results suggest quick and persistent implementation of impulsive vector control strategy.

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ABSTRACT

We develop a mathematical model to closely mimic the integrated program of impulsive vector control (every Friday afternoon since the initiation of the program) and continuous patient treatment and isolation implemented in the Guangdong Province of China during its 2014 dengue outbreak. We fitted the data of accumulated infections and used the parameterized model to carry out a retrospective analysis to estimate the basic reproduction number 1.7425 (95% CI 1.4443–2.0408), the control reproduction number 0.1709, and the mosquito-killing ratios 0.1978, 0.2987, 0.6158 and 0.5571 on October 3, 10, 17 and 24, respectively. This suggests that integrated intervention is highly effective in controlling the dengue outbreak. We also simulated outbreak outcomes under different variations of the implemented interventions. We showed that skipping one Friday for vector control would not result in raising the control reproduction number to the threshold value 1 but would lead to significant increase in the accumulated infections at the end of the outbreak. The findings indicate that quick and persistent impulsive implementation of vector control result in an effective reduction in the control reproduction number and hence lead to significant decline of new infections.

1. Introduction

Dengue is a vector-borne disease in tropical and sub-tropical regions of the world. The disease can be transmitted by the bite of a mosquito infected with one of the four serotypes (Halstead, 2007; Kautner et al., 1997). Since 1978, dengue cases have been reported in China almost every year, with a clear outbreak trend every four to seven years. In June 2014, the dengue cases arose in the Guangdong Province and the case numbers grew exponentially in September of that year (Guangdong Bureau of Health, 2014). By the end of September, the Province had experienced its worst dengue outbreak in over two decades. Near the outbreak peak since September 28, more than 1000 new cases were reported daily (Guangdong Bureau of Health, 2014). On October 23, the total number of the dengue cases exceeded 40,000. According to the National Health and Family Planning Commission (NHFPC), the mosquito population was five times its normal level due to hot and wet weather in South China. This unusual weather, coupled with the increasing mobility, which brought into the province cases contracted abroad, is believed to have contributed to the outbreak (Xinhua News, 2014).

An intensive campaign against the disease outbreak was launched by the end of September, with substantial efforts to reduce mosquitos by sealing puddles of stagnant water, common breeding grounds for the insects (Xinlang News, 2014). Also, according to the Guangdong Province's Public Health Information System which started to make the data of the epidemic public since September 21, the vast majority of infected patients had been hospitalized, reducing

* Corresponding author.
E-mail address: yxiao@mail.xjtu.edu.cn (Y. Xiao).

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the transmission of infected individuals to the vector and accelerating the recovery of hospitalized infectious individuals (Guangdong Bureau of Health, 2014). Shortly after the National Holiday of October 1, the Province implemented its mosquito-killing program, synchronized on every Friday afternoon (specifically, October 3, 10, 17 and 24). It is important to evaluate the effectiveness of this integrated interventions involving impulsive vector culling and human infection isolation and treatment through mathematical modelling and data fitting of surveillance data.

Much progress of modelling dengue infection dynamics including the role of cross-reactive antibodies for the four different dengue serotypes is discussed in Andraud et al. (2012). Early in 1975, Bailey (1975) proposed a basic dengue-transmission dynamics model involving a single serotype, of which the infection dynamics among hosts is described by the classical SIR model and the vector is assumed to remain infectious until death (SI model). Subsequent studies (Esteva and Vargas, 1998; Newton and Reiter, 1992; Tewa et al., 2009) conducted theoretical analyses of this basic model and derived important thresholds to predict disease outcome in the populations. Further and intensive extensions have been considered to address different factors affecting the infection dynamics and disease spread. Wei et al. (2008) assumed direct transmission from infected individuals to susceptible hosts, while Esteva and Vargas (2000), Coutinho et al. (2006), Adams and Boots (2010), and Burattini et al. (2008) proposed models involving vertical transmission among mosquitos. Immunization programs are also evaluated in recent literature including Garba et al. (2008), Supriatna et al. (2008), and Sierra et al. (2010). The role and risk for travellers to and in endemic areas was quantified in Pongsumpun et al. (2004), Messer et al. (2003), Rocco et al. (2001), and Kurane et al. (2000). Age-structured models were used in Erickson et al. (2010), Yang and Ferreira (2008), Luz et al. (2011a,b), and Atkinson et al. (2007) to allow age (or stage)-relevant vector-control measures to be assessed. Johansson et al. (2011) reviewed different approaches that had been used to validate and parameterize dynamic models, of which the basic reproduction numbers for different geographic areas were estimated in Nagao and Koelle (2008), Ferguson et al. (1999), Cummings et al. (2009), Newton and Reiter (1992), Favier et al. (2006), Marques et al. (1994), Massad et al. (2001, 2003), Chowell et al. (2007), Koopman et al. (1991), Coelho et al. (2008), and Degallier et al. (2009). To our best knowledge, there is a gap to develop and analyze models that depict the kind of integration of interventions involving impulsive mosquito killing and human case treatment, and to use these models to inform the effective vector-killing rate from human surveillance and to evaluate the effectiveness of these vector-control efforts to suggest alternative measures for future outbreaks.

In our current work, we extend the basic dengue-transmission dynamics model by explicitly incorporating hospitalized individuals as a separate compartment with recovery and transmission rates distinct from those infected individuals. Similar to Yang and Ferreira (2008), Esteva and Vargas (2000), Coutinho et al. (2006), and Burattini et al. (2008), we also extend the basic dengue-transmission model by taking the exposed compartment of mosquitos into consideration. To further evaluate control measures involving the application of insecticides as airborne sprays to kill adult mosquitos using portable or truck-mounted machines in Guangdong Province, we expand the dynamics model by considering impulsive control, in comparison with those (Yang and Ferreira, 2008; Luz et al., 2011b; Atkinson et al., 2007; Burattini et al., 2008) where control strategies are assumed to be implemented continuously.

2. The model involving integrated control strategies

In our model framework, the total female mosquito population at time t, denoted by $N_m(t)$, is split into subpopulations of susceptible ($S_m(t)$), exposed ($E_m(t)$) and infected ($I_m(t)$) mosquitos. The susceptible mosquitos move to the latent compartment E_m via the infection. The birth rate of mosquitos is given by constant Λ, and mosquitos are diminished by a natural death rate μ_m. The mosquitos surviving their latent period $(1/\sigma)$ become infectious. Similarly, the human population at time t, denoted by $N_h(t)$, is split into the subpopulations of susceptible ($S_h(t)$), infected ($I_h(t)$), hospitalized ($H_h(t)$) and recovered ($R_h(t)$). A susceptible individual exposed to the infected mosquito becomes infectious if infected. We assume that a portion of infected individuals is hospitalized, although our model also allows infected individuals become recovered before being hospitalized. The model thus takes the following format:

$$\begin{aligned}\frac{dS_h}{dt} &= \mu_h N_h - c\beta_{mh}\frac{I_m}{N_h}S_h - \mu_h S_h,\ \frac{dI_h}{dt}\\ &= c\beta_{mh}\frac{I_m}{N_h}S_h - (\gamma_1+\gamma_2)I_h - \mu_h I_h,\ \frac{dH_h}{dt} = \gamma_1 I_h - \gamma_3 H_h - \mu_h H_h,\ \frac{dR_h}{dt}\\ &= \gamma_2 I_h + \gamma_3 H_h - \mu_h R_h,\ \frac{dS_m}{dt} = \Lambda - c\beta_{hm}\frac{I_h}{N_h}S_m - \mu_m S_m,\ \frac{dE_m}{dt}\\ &= c\beta_{hm}\frac{I_h}{N_h}S_m - \mu_m E_m - \sigma E_m,\ \frac{dI_m}{dt} = \sigma E_m - \mu_m I_m.\end{aligned} \tag{1}$$

Here c is the average biting rate of the mosquitos, β_{hm} and β_{mh} are the transmission probabilities from human to mosquitos and from mosquitos to human, respectively, and γ_1 is the hospitalization rate of infected individuals, γ_2 and γ_3 are recovery rates of infected and hospitalized individuals, respectively. Because only six cases were reported to die due to the infection of dengue during the 2014 dengue outbreak in Guangdong province (Xiao et al., 2016), we do not consider the disease related death in model (1). Furthermore, the course of dengue is fairly short compared to human life span, we thus assume that the population remain a constant size with equivalent natural birth and death rate, denoted by constant μ_h (Esteva and Vargas, 1998; Tewa et al., 2009). Definitions of model parameters and variables are also listed in Table 1. Note that the total

Table 1
Definitions of the parameters and variables.

	Definitions	Baseline values	References
Variables			
S_h	Susceptible hosts	–	
I_h	Infectious hosts	–	
H_h	Infectious hosts in hospital	–	
R_h	Recovered hosts	–	
S_m	Susceptible mosquitos	–	
E_m	Exposed mosquitos	–	
I_m	Infectious mosquitos	–	
Parameters			
μ_h	Host natural mortality rate (day^{-1})	3.5×10^{-5}	Burattini et al. (2008)
μ_m	Mosquito natural mortality rate (day^{-1})	0.05–0.25	Andraud et al. (2012)
γ_1	Hospitalization rate	Unknown	
γ_2	Host recovery rate (infectious individuals) (day^{-1})	0.071–0.33	Andraud et al. (2012)
γ_3	Host recovery (hospitalized individuals)	Unknown	
c	Biting rate (per mosquito per day) (day^{-1})	0.3–1	Andraud et al. (2012)
β_{mh}	Mosquito-to-human transmission probability	Unknown	
β_{hm}	Human-to-mosquito transmission probability	Unknown	
σ	Mosquito incubation rate (day^{-1})	1/7	Burattini et al. (2008)
Λ	Constant birth rate of mosquitos	Unknown	

number of human individuals is a constant N_h, and the total number of mosquitos approaches $\hat{N}_m = \Lambda/\mu_m$.

Using the next-generation matrix introduced in Diekmann and Heesterbeek (2000) and van den Driessche and Watmough (2002), the basic reproduction number of model (1) has been calculated (see Appendix A for details), denoted by R_0, which is the spectral radius of the next generation matrix and given by

$$R_0 = \sqrt{c^2\beta_{hm}\beta_{mh}\frac{1}{\gamma_1+\gamma_2+\mu_h}\frac{\sigma}{\mu_m+\sigma}\frac{1}{\mu_m}\frac{\hat{N}_m}{N_h}}. \tag{2}$$

Note that this threshold can also be calculated following the alternate method developed by Heesterbeek and Roberts (Heesterbeek and Roberts, 2007; Roberts and Heesterbeek, 2003). Then the type-reproduction number of infected individuals, which determines the critical control effort for heterogeneous populations, gives

$$T_0 = \frac{c\beta_{mh}\sigma}{(\mu_m+\sigma)\mu_m}\cdot\frac{c\beta_{hm}\hat{N}_m}{(\gamma_1+\gamma_2+\mu_h)N_h}. \tag{3}$$

In fact, T_0 has an epidemiological interpretation. $c\beta_{mh}\sigma/((\mu_m+\sigma)\mu_m)$ is the average number of secondary infectious individuals generated by an infected mosquito during its mean infectious time, $c\beta_{hm}\hat{N}_m/((\gamma_1+\gamma_2+\mu_h)N_h)$ the average numbers of secondary infectious mosquitos generated by an infectious host during his/her mean infectious time, respectively. So T_0 is the expected number of secondary infectious hosts generated by an infectious host during her mean infectious time.

started on October 3 (Friday), and subsequently in the afternoon of every Friday until October 24 within a relative short period. Therefore, there are four times of vector control actions taken by the Guangdong government to reduce the density of mosquitos during the 2014 dengue outbreak. For simplification, we assume that the control actions have been taken instantaneously and denote the killing rates on October 3, 10, 17 and 24 as p_i $(i = 1, 2, 3, 4)$, respectively. In order to investigate the effectiveness of the vector control actions by comparing the control reproduction number with the basic reproduction number, we further extend model (1) to a periodic impulsive system with a period of 28 days (four weeks), which allows us to determine the control reproduction number. To do this, we let October 3 be the initial time of the impulsive system and denote it as $\tau_0^1 = 0$, consequently we denote October 10, 17 and 24 as $\tau_0^2 = T$, $\tau_0^3 = 2T$ and $\tau_0^4 = 3T$ with $T=7$ (days), respectively. Similarly, for the next period of 28 days we have that four action times of killing mosquitos are $\tau_1^i = (4 + i - 1)T$, $i = 1, 2, 3, 4$, with killing ratios p_i, respectively. Generally, for any one period we can define four times of the vector control actions as $\tau_n^i = (4n + i - 1)T$, $i = 1, 2, 3, 4$, with killing rates p_i for $n \in \mathcal{N}$ with $\mathcal{N} = \{0, 1, 2, \ldots\}$, which means that $\tau_{n+1}^i = \tau_n^i + 28$, $i = 1, 2, 3, 4$. Based on the above discussions we have the following impulsive model:

$$\left.\begin{aligned}
\frac{dS_h}{dt} &= \mu_h N_h - c\beta_{mh}\frac{I_m}{N_h}S_h - \mu_h S_h,\\
\frac{dI_h}{dt} &= c\beta_{mh}\frac{I_m}{N_h}S_h - (\gamma_1+\gamma_2)I_h - \mu_h I_h,\\
\frac{dH_h}{dt} &= \gamma_1 I_h - \gamma_3 H_h - \mu_h H_h,\\
\frac{dR_h}{dt} &= \gamma_2 I_h + \gamma_3 H_h - \mu_h R_h,\\
\frac{dS_m}{dt} &= \Lambda - c\beta_{hm}\frac{I_h}{N_h}S_m - \mu_m S_m,\\
\frac{dE_m}{dt} &= c\beta_{hm}\frac{I_h}{N_h}S_m - \mu_m E_m - \sigma E_m,\\
\frac{dI_m}{dt} &= \sigma E_m - \mu_m I_m,
\end{aligned}\right\} t \neq \tau_n^1, \tau_n^2, \tau_n^3, \tau_n^4,
\left.\begin{aligned}
S_m((4n+i-1)T^+) &= (1-p_i)S_m((4n+i-1)T),\\
E_m((4n+i-1)T^+) &= (1-p_i)E_m((4n+i-1)T),\\
I_m((4n+i-1)T^+) &= (1-p_i)I_m((4n+i-1)T),
\end{aligned}\right\} t = \tau_n^i, \quad i = 1, 2, 3, 4. \tag{4}$$

To discuss the existence of the infection-free periodic solution for system (4), we let $I_h = H_h = R_h = E_m = I_m = 0$. And then system (4) becomes the following subsystem:

$$\left.\begin{aligned}
\frac{dS_h}{dt} &= 0,\\
\frac{dS_m}{dt} &= \Lambda - \mu_m S_m,
\end{aligned}\right\} t \neq \tau_n^1, \tau_n^2, \tau_n^3, \tau_n^4,
\left.\begin{aligned}
S_h((4n+i-1)T^+) &= S_h((4n+i-1)T),\\
S_m((4n+i-1)T^+) &= (1-p_i)S_m((4n+i-1)T),
\end{aligned}\right\} t = \tau_n^i, \quad i = 1, 2, 3, 4. \tag{5}$$

As mentioned in the introduction, after the outbreak in the province, a series of measures were implemented to control the infection dynamics, of which killing mosquitos was a main component. In particular, every Friday afternoon was chosen as the fixed time to carry out the synchronized action of killing mosquitos. October 1 is a national holiday and there was huge human population mobility, so the governments enhanced control strategies and the campaign of killing mosquitos

It follows from model (5) that S_h and S_m are independent while $\bar{S}_h = N_h$ is a trivial periodic solution for the above equations. Thus, we only need to consider the following system:

$$\begin{aligned}
\frac{dS_m}{dt} &= \Lambda - \mu_m S_m,\ t \neq \tau_n^1, \tau_n^2, \tau_n^3, \tau_n^4,\ S_m((4n+i-1)T^+)\\
&= (1-p_i)S_m((4n+i-1)T),\ t = \tau_n^i, \quad i = 1, 2, 3, 4.
\end{aligned} \tag{6}$$

Solving the first equation of model (6) in the interval $(4nT, (4n+1)T]$ gives

$$S_m(t) = \left(S_m(4nT^+) + \frac{\Lambda}{\mu_m}(e^{\mu_m(t-4nT)} - 1)\right)e^{-\mu_m(t-4nT)}. \tag{7}$$

Thus, we have

$$S_m((4n+1)T) = \left(S_m(4nT^+) + \frac{\Lambda}{\mu_m}(e^{\mu_m T} - 1)\right)e^{-\mu_m T}, \tag{8}$$

which means that

$$S_m((4n+1)T^+) = (1-p_2)\left(S_m(4nT^+) + \frac{\Lambda}{\mu_m}(e^{\mu_m T} - 1)\right)e^{-\mu_m T}. \tag{9}$$

Repeating the process yields

$$S_m((4n+2)T^+) = (1-p_3)\left(S_m((4n+1)T^+) + \frac{\Lambda}{\mu_m}(e^{\mu_m T} - 1)\right)e^{-\mu_m T}. \tag{10}$$

$$S_m((4n+3)T^+) = (1-p_4)\left(S_m((4n+2)T^+) + \frac{\Lambda}{\mu_m}(e^{-\mu_m T} - 1)\right)e^{-\mu_m T}. \tag{11}$$

$$S_m((4n+4)T^+) = (1-p_1)\left(S_m((4n+3)T^+) + \frac{\Lambda}{\mu_m}(e^{\mu_m T} - 1)\right)e^{-\mu_m T}. \tag{12}$$

Combining Eqs. (9)–(12) yields

$$\begin{aligned} S_m((4n+4)T^+) = {} & (1-p_1)(1-p_2)(1-p_3)(1-p_4) \\ & e^{-4\mu_m T}S_m(4nT^+) + \frac{\Lambda}{\mu_m}(e^{\mu_m T} - 1) \\ & \Big((1-p_1)e^{-\mu_m T} + (1-p_1)(1-p_4)e^{-2\mu_m T} \\ & + (1-p_1)(1-p_4)(1-p_3)e^{-3\mu_m T} + (1-p_1) \\ & (1-p_4)(1-p_3)(1-p_2)e^{-4\mu_m T}\Big). \end{aligned} \tag{13}$$

Solving the fixed point of Eq. (13), we have

$$\begin{aligned} S_m^1 = {} & \left(\begin{array}{l} (1-p_1)e^{3\mu_m T} + (1-p_1)(1-p_4)e^{2\mu_m T} + (1-p_1) \\ \dfrac{(1-p_4)(1-p_3)e^{\mu_m T} + (1-p_1)(1-p_4)(1-p_3)(1-p_2)}{e^{4\mu_m T} - (1-p_1)(1-p_2)(1-p_3)(1-p_4)} \end{array}\right) \\ & \frac{\Lambda}{\mu_m}(e^{\mu_m T} - 1). \end{aligned} \tag{14}$$

Let

$$\begin{aligned} S_m^2 &= (1-p_2)\left(S_m^1 + \frac{\Lambda}{\mu_m}(e^{\mu_m T} - 1)\right)e^{-\mu_m T}, S_m^3 \\ &= (1-p_3)\left(S_m^2 + \frac{\Lambda}{\mu_m}(e^{\mu_m T} - 1)\right)e^{-\mu_m T}, S_m^4 \\ &= (1-p_4)\left(S_m^3 + \frac{\Lambda}{\mu_m}(e^{\mu_m T} - 1)\right)e^{-\mu_m T}. \end{aligned} \tag{15}$$

Then we can conclude that there is a periodic solution of system (6), denoted by $\bar{S}_m(t)$ with

$$\bar{S}_m(t) = \begin{cases} S_m(t) = \left(S_m^1 + \frac{\Lambda}{\mu_m}(e^{\mu_m(t-4nT)} - 1)\right)e^{-\mu_m(t-4nT)}, \\ \quad t \in \left(4nT, (4n+1)T\right], \\ S_m(t) = \left(S_m^2 + \frac{\Lambda}{\mu_m}(e^{\mu_m(t-(4n+1)T)} - 1)\right)e^{-\mu_m(t-(4n+1)T)}, \\ \quad t \in \left((4n+1)T, (4n+2)T\right], \\ S_m(t) = \left(S_m^3 + \frac{\Lambda}{\mu_m}(e^{\mu_m(t-(4n+2)T)} - 1)\right)e^{-\mu_m(t-(4n+2)T)}, \\ \quad t \in \left((4n+2)T, (4n+3)T\right], \\ S_m(t) = \left(S_m^4 + \frac{\Lambda}{\mu_m}(e^{\mu_m(t-(4n+3)T)} - 1)\right)e^{-\mu_m(t-(4n+3)T)}, \\ \quad t \in \left((4n+3)T, (4n+4)T\right]. \end{cases} \tag{16}$$

Thus, system (4) admits an infection-free periodic solution $\bar{\xi}(t) = (\bar{S}_h, 0, 0, 0, \bar{S}_m(t), 0, 0)$ with period $4T$.

To investigate the stability of the infection-free periodic solution $\bar{\xi}(t)$ we applied the Floquet theory (Bainov and Simeonov, 1989, 1993). Let $x_1(t) = S_h(t) + \bar{S}_h$, $x_2(t) = I_h(t)$, $x_3(t) = H_h(t)$, $x_4(t) = R_h(t)$, $x_5(t) = S_m(t) + \bar{S}_m(t)$, $x_6(t) = E_m(t)$, $x_7(t) = I_m(t)$, then

$$X(t) = (x_1(t), x_2(t), x_3(t), x_4(t), x_5(t), x_6(t), x_7(t))$$

can be represented as the following:

$$X(t) = \Phi_1(t)X(0),\ t \in [0, 4T), \tag{17}$$

where $\Phi_1(t)$ satisfies the following differential equations:

$$\frac{d\Phi_1(t)}{dt} = \begin{pmatrix} 0 & \mu_h & \mu_h & \mu_h & 0 & 0 & -c\beta_{mh} \\ 0 & -\gamma_1-\gamma_2-\mu_h & 0 & 0 & 0 & 0 & c\beta_{mh} \\ 0 & \gamma_1 & -\gamma_3-\mu_h & 0 & 0 & 0 & 0 \\ 0 & \gamma_2 & \gamma_3 & -\mu_h & 0 & 0 & 0 \\ 0 & -c\beta_{hm}\dfrac{\bar{S}_m(t)}{N_h} & 0 & 0 & -\mu_m & 0 & 0 \\ 0 & c\beta_{hm}\dfrac{\bar{S}_m(t)}{N_h} & 0 & 0 & 0 & -\mu_m-\sigma & 0 \\ 0 & 0 & 0 & 0 & 0 & \sigma & -\mu_m \end{pmatrix}\Phi_1(t) \tag{18}$$

and $\Phi_1(0) = I$, I is the identity matrix.

Denote

$$P_i = \begin{pmatrix} E_{4\times4} & \mathbf{0}_{4\times3} \\ \mathbf{0}_{3\times4} & p_i{*}E_{3\times3} \end{pmatrix}, \quad i = 1, 2, 3, 4, \tag{19}$$

and let

$$M_1 = P_1P_2P_3P_4\Phi_1(4T).$$

Then the stability of the infection-free periodic solution $\bar{\xi}(t)$ is decided by the eigenvalues of the monodromy matrix M_1. Let μ_i, $i = 1, 2, \ldots, 7$, be the eigenvalues of the monodromy matrix M_1. If $|\mu_i| \neq 1$, $i = 1, \ldots, 7$, then we define $R_0^{G_1} = \rho(M_1)$, where $\rho(M_1)$ is the spectral radius of the matrix M_1, and we can conclude when $R_0^{G_1} < 1$, the infection-free periodic solution $\bar{\xi}(t)$ is locally asymptotically stable; when $R_0^{G_1} > 1$, the infection-free periodic solution $\bar{\xi}(t)$ is unstable. Otherwise, let $R_0^{G_1} = \max\{|\mu_j|: |\mu_j| \neq 1\}$. Then if the duplicate number of characteristic root is equal to one for all the eigenvalues of which the absolute values are equal to 1, we have that the infection-free periodic solution $\bar{\xi}(t)$ is locally stable when $R_0^{G_1} < 1$ and the infection-free periodic solution $\bar{\xi}(t)$ is unstable when $R_0^{G_1} > 1$.

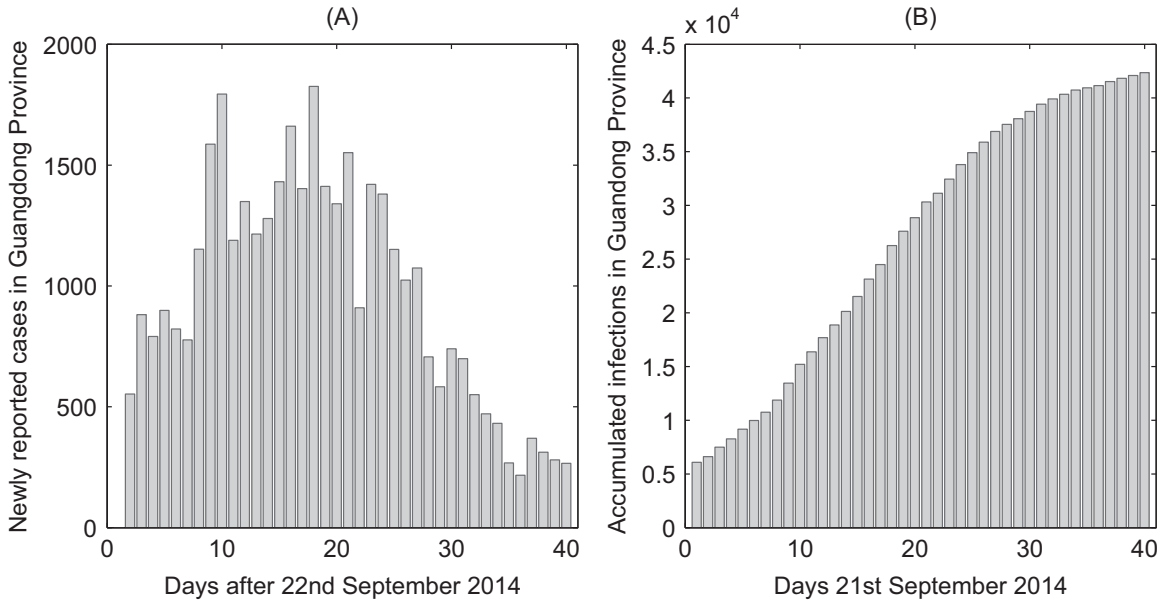

Fig. 1. The reported cases of dengue for the province of Guangdong.

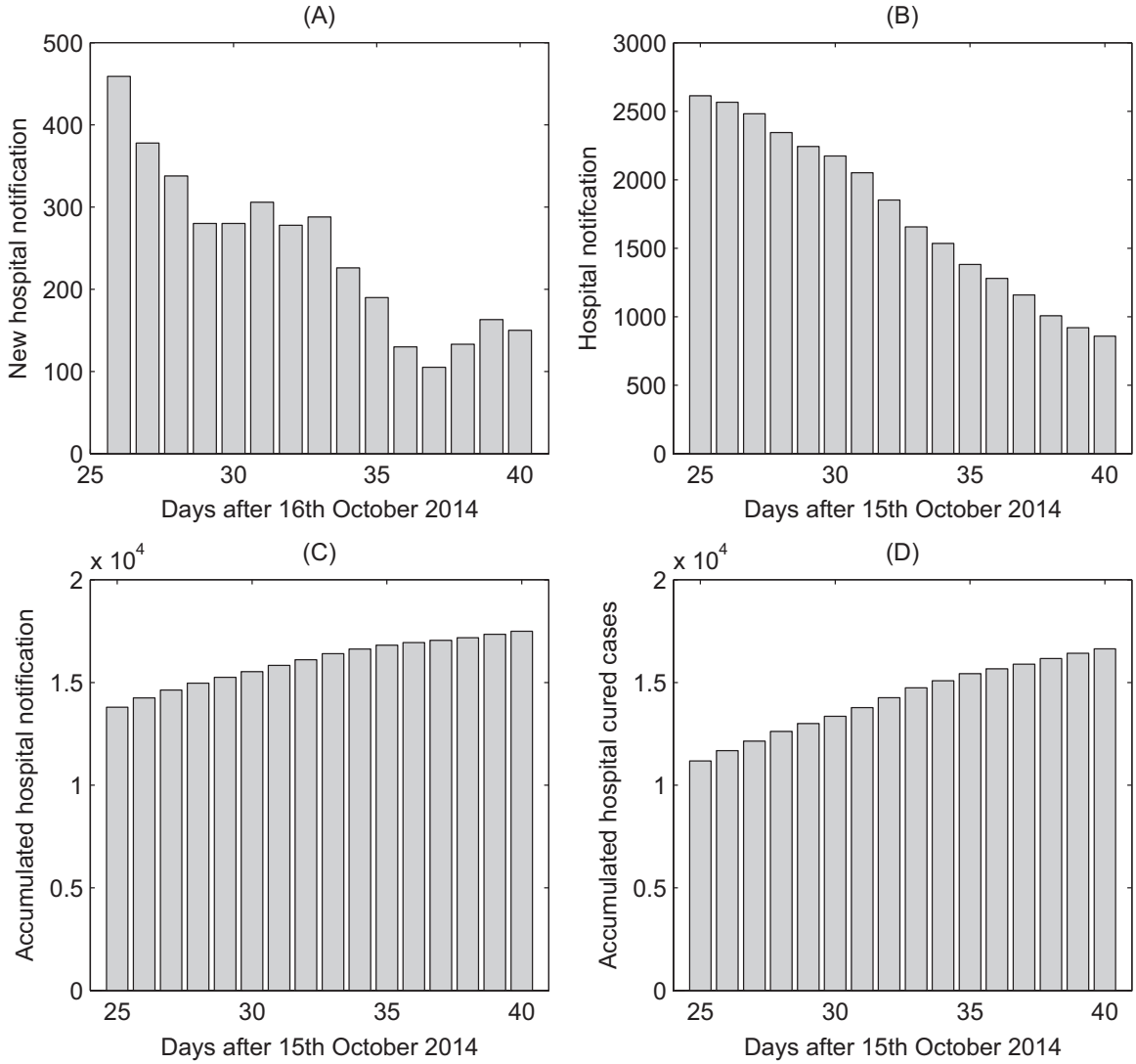

Fig. 2. Daily number of hospital notifications for the province of Guangdong.

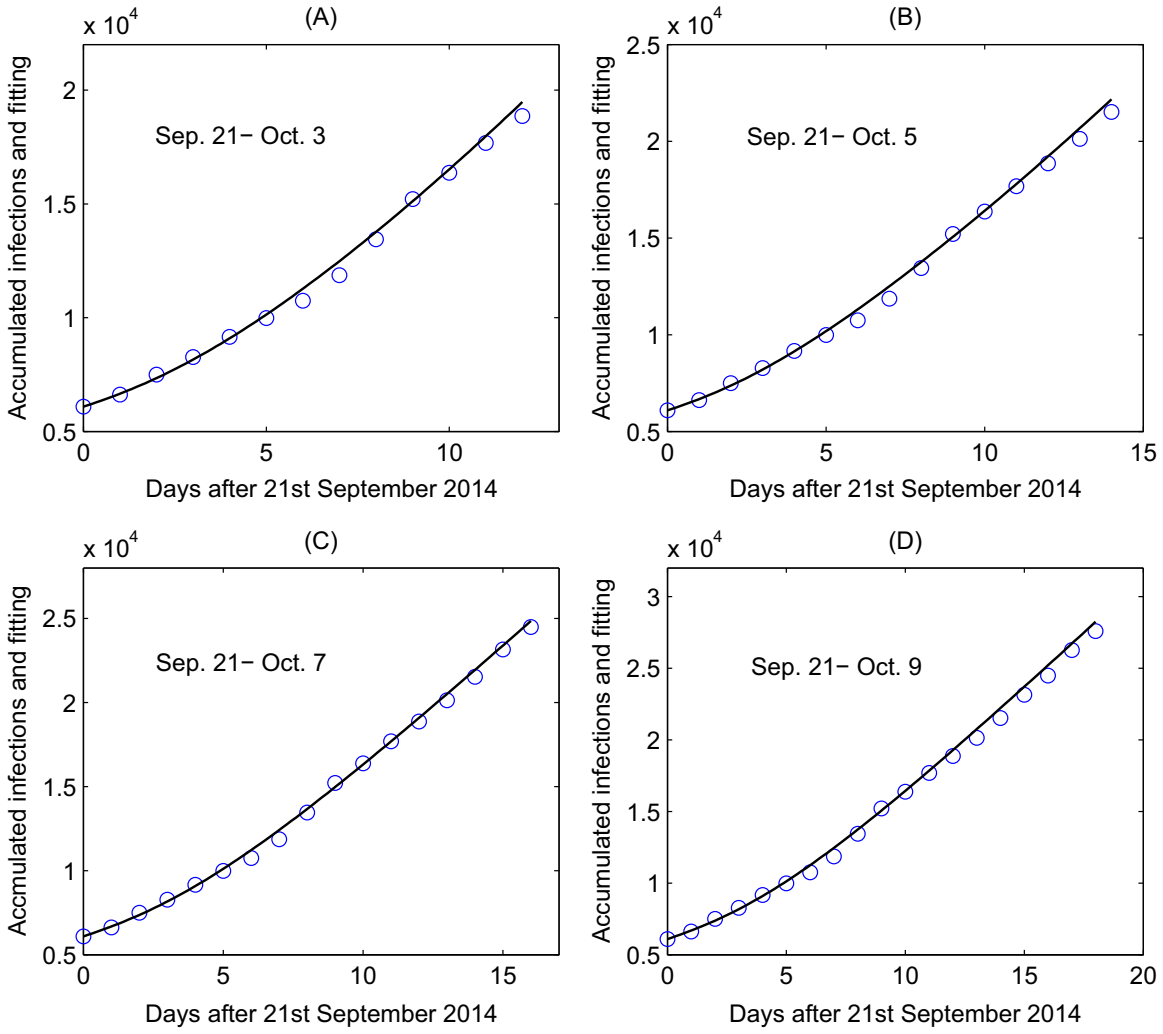

Fig. 3. Data fitting for four time intervals: (A) from 21 September to 3 October; (B) from 21 September to 5 October; (C) from 21 September to 7 October; (D) from 21 September to 9 October. The blue circles represent the accumulated infections in the province of Guangdong and the black curves are the fitting curves. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this paper.)

Table 2
Parameter estimates based on the data of the accumulated infections after 21 September.

Parameter	September 21–October 3		September 21–October 5		September 21–October 7		September 21–October 9	
	Mean	Std	Mean	Std	Mean	Std	Mean	Std
$I_h(0)$	14,646	3501	16,628	2696	34,857	3881	37,812	6173
$H_h(0)$	2004	579	1995	575	2029	578	1734	432
$S_m(0)$	8×10^7	2.89×10^6	7.81×10^7	4.26×10^6	7.93×10^7	6.95×10^6	8.01×10^7	2.86×10^6
$E_m(0)$	21,230	3708	21,478	3792	280,64	4250	27,419	4283
$I_m(0)$	17,998	4101	17,956	4095	44,318	7114	48,899	9416
γ_1	0.5549	0.13392	0.6695	0.1601	0.43126	0.0849	0.3666	0.0758
γ_3	0.0812	0.0406	0.2251	0.1005	0.12357	0.0430	0.2252	0.1007
Λ	9.76×10^6	4.35×10^5	9.7×10^6	4.3×10^5	9.73×10^6	4.29×10^5	9.75×10^6	4.3×10^5
β_{mh}	0.0385	0.0065	0.0393	0.0064	0.0167	0.0020	0.0155	0.0024
β_{hm}	0.6759	0.1217	0.6465	0.1460	0.6970	0.1013	0.6512	0.1201

3. Estimation of the control reproduction number R_0^G

3.1. Data

We obtained data on laboratory-confirmed cases of dengue fever in the province of Guangdong, China, from the province's Public Health Information System. The information system contains data about the cumulative number of reported cases and the

Table 3
Estimations of R_0 for four intervals.

From	To	R_0	95% CI of R_0
September 21	October 3	1.7425	(1.4443,2.0408)
September 21	October 5	1.5830	(1.3788,1.7873)
September 21	October 7	1.2869	(1.1510,1.4227)
September 21	October 9	1.2656	(1.1118,1.4193)

Table 4
Estimates for the control parameters and $R_0^{C_1}$.

Paramters	Estimation values	Sensitive analysis of $R_0^{C_1}$ with different control parameter values								
p_1	0.1978	0	0.1978	0.1978	0.1978	0	0	0	0	0
p_2	0.2987	0.2987	0	0.2987	0.2987	0	0.2987	0	0	0
p_3	0.6158	0.6158	0.6158	0	0.6158	0	0	0.6158	0	0
p_4	0.5571	0.5571	0.5571	0.5571	0	0	0	0	0.5571	0
$R_0^{C_1}$	0.1709	0.2245	0.2467	0.4796	0.4181	2.9847	2.3257	0.9275	1.1133	4.7879

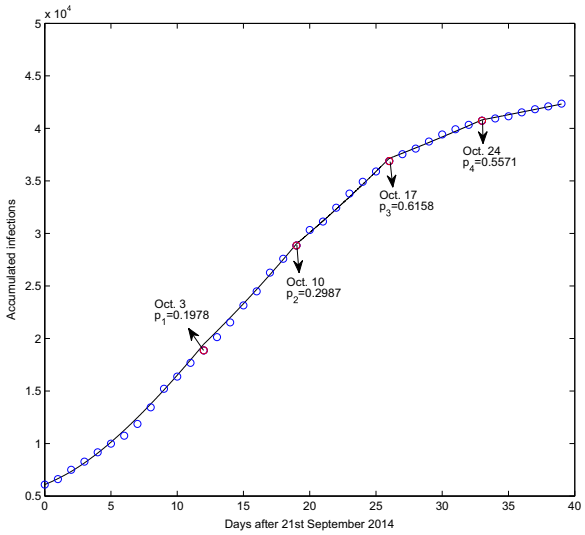

Fig. 4. Goodness of fit. Fitting model (B.3) to the accumulated infections in the province of Guangdong (Circles) from 21 September to 30 October 2014.

number of new cases, as shown in Fig. 1. On September 21, 2014, local cases were found and reported in the city Foshan. Guangdong Bureau of Health (GBH) started to report cases daily. Since October 15, GBH started also to report hospital notifications, the cumulative number of treated and cured cases, as shown in Fig. 2. Some of the confirmed cases in the province were hospitalized with treatments, and we assume that these cases were unable to transmit to mosquitos.

3.2. Estimation of reproduction number

To estimate the parameters, the mean survival time of a mosquito has been fixed at 21 days, which means that $\mu_m = 1/21$ (Andraud et al., 2012). An individual can recover for about 7 days ($\gamma_2 = 0.143$) on average after infected (Burattini et al., 2008). The biting rate and the incubation rate of mosquitos are fixed at 0.76 (Scott et al., 2000) and 1/7 (Burattini et al., 2008), respectively. As mentioned before, the total number of humans is a constant. The infection of dengue in Guangdong Province mainly happened in the cities Guangzhou, Foshan and Zhongshan, and the total number of humans of those three cities is 23,396,400. Therefore, we fixed the total population of humans at 23,396,400; that is $N_h \approx 23,396,400$.

It is worth noting that, at the beginning of the outbreak in Guangdong Province, the ratio S_h/N_h is approximately equal to 1. Therefore, with proper assumptions, model (1) has been simplified as model (B.2); see details in Appendix B. To carry out the Markov chain Monte Carlo (MCMC) procedure, an adaptive Metropolis–Hastings (M–H) algorithm has been used (Haario et al., 2006). We first estimated the unknown parameters and initial values and their standard deviations on the basis of model (B.2), and then

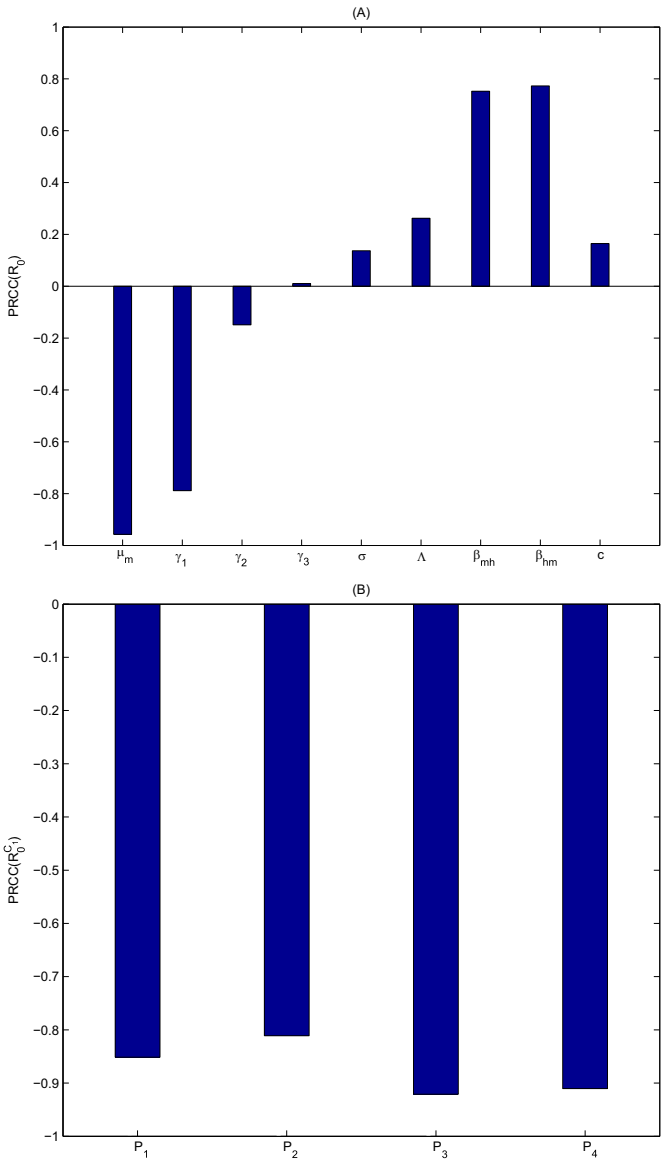

Fig. 5. Sensitivity analysis. (A) PRCCs of R_0 for all the parameters of model (B.2) and (B) PRCC of $R_0^{C_1}$ with respect to the control parameters p_1, p_2, p_3 and p_4.

estimated the basic reproduction number R_0. The algorithm was run for 500,000 iterations with a burn-in of 500,000 iterations, and the Geweke convergence diagnostic method was employed to assess convergence of chains (Geweke et al., 1992).

By fitting model (1) to the data of accumulated infections after September 21, as shown in Fig. 3, we estimated key epidemic parameters and initial conditions in each of subpopulations of hosts and vectors, as listed in Table 2. We also used the data of accumulated infections between September 21 and October 3 to

estimate the mean basic reproduction number as 1.7425 (95% CI 1.4443–2.0408). Replacing October 3 by October 5, 7 and 9 for the endpoint when massive interventions might have altered the transmission dynamics, we examined the sensitivity of the basic reproduction number with respect to the time interval considered and observed that this number varied between 1.2656 and 1.7425, as listed in Table 3. Note that, when different periods are considered, the estimated mean initial numbers of infected humans and mosquitos have a large range, from 14,646 to 37,812 and from 17,998 to 48,899, respectively. However, the initial values for other compartments of humans and mosquitos are not very sensitive to the period.

In order to estimate the ratios of killing mosquitos on these Fridays (p_1, p_2, p_3 and p_4), we further simplify model (4) as model (B.3), see Appendix B for details. In particular, before October 3, interventions as outlined above were ignored, and the impulsive model (B.3) actually becomes model (B.2). Therefore, all the parameter values in model (B.2) are fixed as the same as those estimated on the basis of data of accumulated infections from September 21 to October 3 (see details in Table 2). Then, based on the data of accumulated infections from October 3 to October 30, we estimated all the control parameters as follows:

$$p_1 = 0.1978, \quad p_2 = 0.2987, \quad p_3 = 0.6158, \quad p_4 = 0.5571$$

(see Table 4). The data fitting, using the least-squares method, is shown in Fig. 4. Finally, we can calculate the control reproduction number $R_0^{C_1}$ as 0.1709. Note that this number is far below the unity, and hence the integrated control in the province contributed to significant reduction of the infection reproduction.

3.3. Sensitivity analysis and effectiveness of vector control

We explored the parameter space by performing an uncertainty analysis using a Latin hypercube sampling method. We used a partial rank correlation coefficients (PRCCs) (Mckay et al., 1979; Blower and Dowlatabadi, 1994; Marino et al., 2008; Tang et al., 2012) to examine the sensitivity analysis for R_0 and $R_0^{C_1}$ with respect to involved parameters and all control parameters, respectively. In the absence of data to inform distribution functions, we chose a normal distribution for all input control parameters

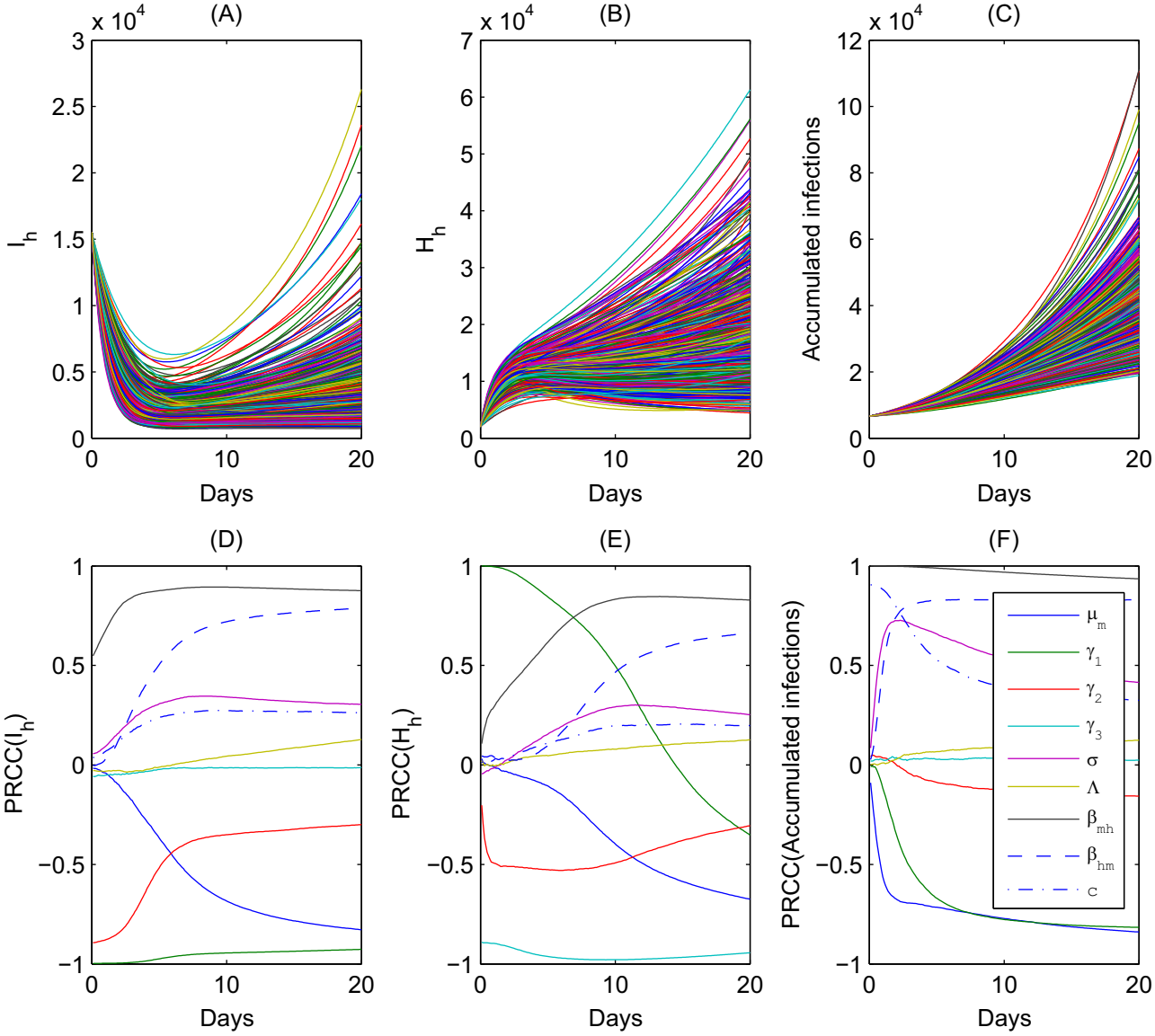

Fig. 6. Sensitivity analysis. (A), (B) and (C) are plots of outputs (1000 runs) of model (B.2) for infected humans, hospitalized individuals and accumulated infections, respectively. (D)–(F) PRCC of the nine parameters for (D) the number of infected humans, (E) the number of hospitalized humans and (F) the number of accumulated infections over 20 days.

with mean value and standard deviation. The PRCC values for R_0 and $R_0^{C_1}$ are shown in Fig. 5. Fig. 5(A) indicates that the first four parameters with most impact on the R_0 are mosquito-to-human/human-to-mosquito transmission probability, mosquito natural mortality rate μ_m and the hospitalization rate γ_1. It follows from Fig. 5(B) that these control parameters are all negatively correlated with very large PRCCs. This confirms that the mosquito killing on each Friday during the specified period did play an important role in controlling the dengue outbreak.

We performed the sensitive analysis of infected humans, hospitalized individuals and accumulated infections through evaluating the PRCCs with respect to all the parameters of model (B.2) over time by choosing a normal distribution with mean value and standard deviation shown in Fig. 6. Fig. 6(A)–(C) shows the 1000 outputs of model (B.2) for infected humans, hospitalized individuals and accumulated infections corresponding to the LHS matrix and scheme defined by varying all input parameters. In Fig. 6(D)–(F), we plotted the PRCCs over time with respect to the infected humans, hospitalized individuals and accumulated infections, respectively. Fig. 6(D) indicates that there are four PRCC values that are significantly different from zero and the PRCC values of these four examined parameters stabilize at fixed values around 20 days. The first four parameters with most impact on the outcome (the number of infected humans) are the mosquito-to-human/human-to-mosquito transmission probability, mosquito natural mortality rate μ_m and the hospitalization rate γ_1, which is in agreement with the PRCC values for R_0, as shown in Fig. 5(A).

To further assess the impact and necessity of the mosquito-culling campaign, we simulated the outbreak outcome under different scenarios. We calculated the control reproduction number $R_0^{C_1}$ when mosquito culling was not implemented on one of the four Fridays. The simulations are reported in Table 4. We observe that $R_0^{C_1}$ can still be reduced to a level under the unity so the epidemic can be controlled, even if the mosquito killing was skipped for one of the Fridays. However, Fig. 7(A) shows that the mosquito killing on October 17 is most critical in terms of reduction of the control reproduction number $R_0^{C_1}$ and the size of accumulated infections till October 30 (shown in pink curve). On the other hand, the role of mosquito killing on the first Friday (October 3) is twofold: the reduction in control reproduction number $R_0^{C_1}$ is the smallest one, but reduction in the size of accumulated infections is not. We also considered the situation when the mosquito killing is implemented only on one of the four Fridays. Simulations are reported in Fig. 7(B), where the corresponding solutions of model (B.3) are plotted, and the corresponding control reproduction numbers are calculated and listed in Table 4. The calculation shows that mosquito killing alone on October 17 is sufficient to reduce the control reproduction number below 1. Note that the mosquito killing ratio on October 17 is the biggest.

We further compared the outbreak outcomes with other plausible modification of the vector-control strategies; Fig. 8 (A) displays the model solutions with different mosquito-killing ratios on October 3, while Fig. 8(B) displays the solutions when vector-control is implemented only on one of the four Fridays. Unlike simulations in Fig. 7(B), here we used a fixed mosquito-killing ratio of 0.4. The simulations show that earlier

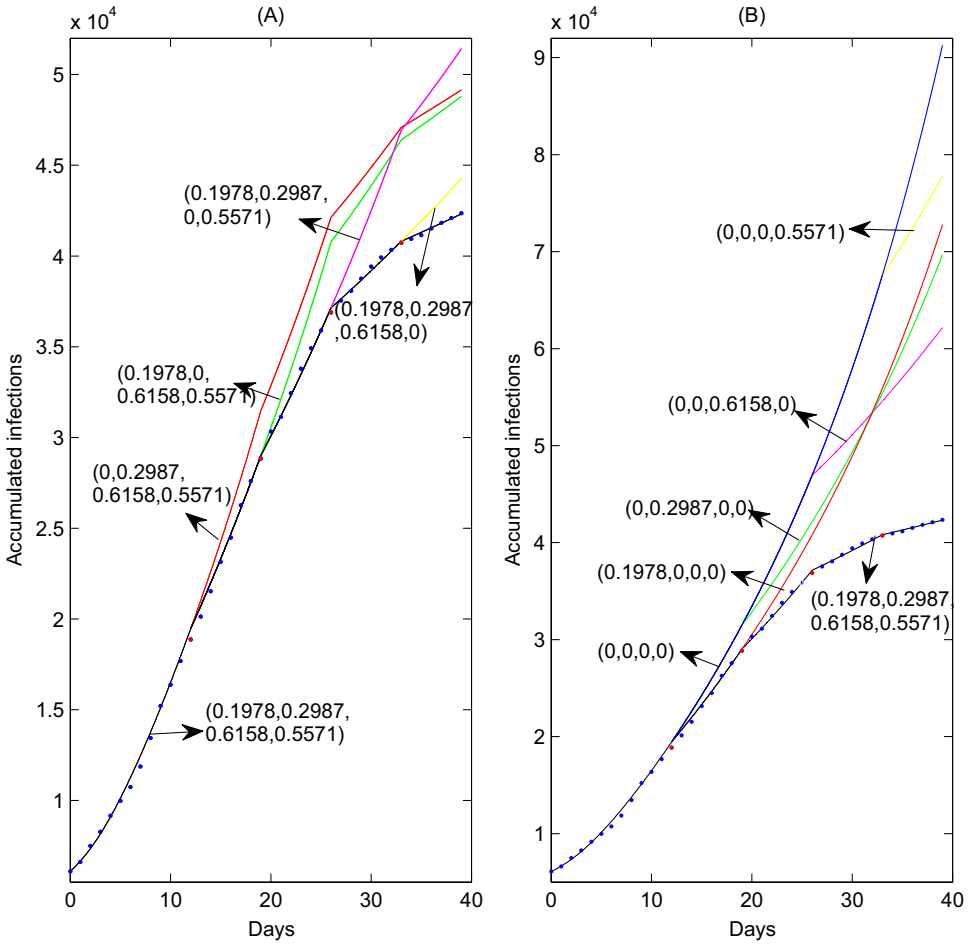

Fig. 7. The effectiveness analysis with different choices of the implementations of killing mosquitos. (A) Solutions of model (B.3) if one of these four times of killing mosquitos is absent; (B) solutions to model (B.3) if just one of these four times of killing mosquitos is carried out. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this paper.)

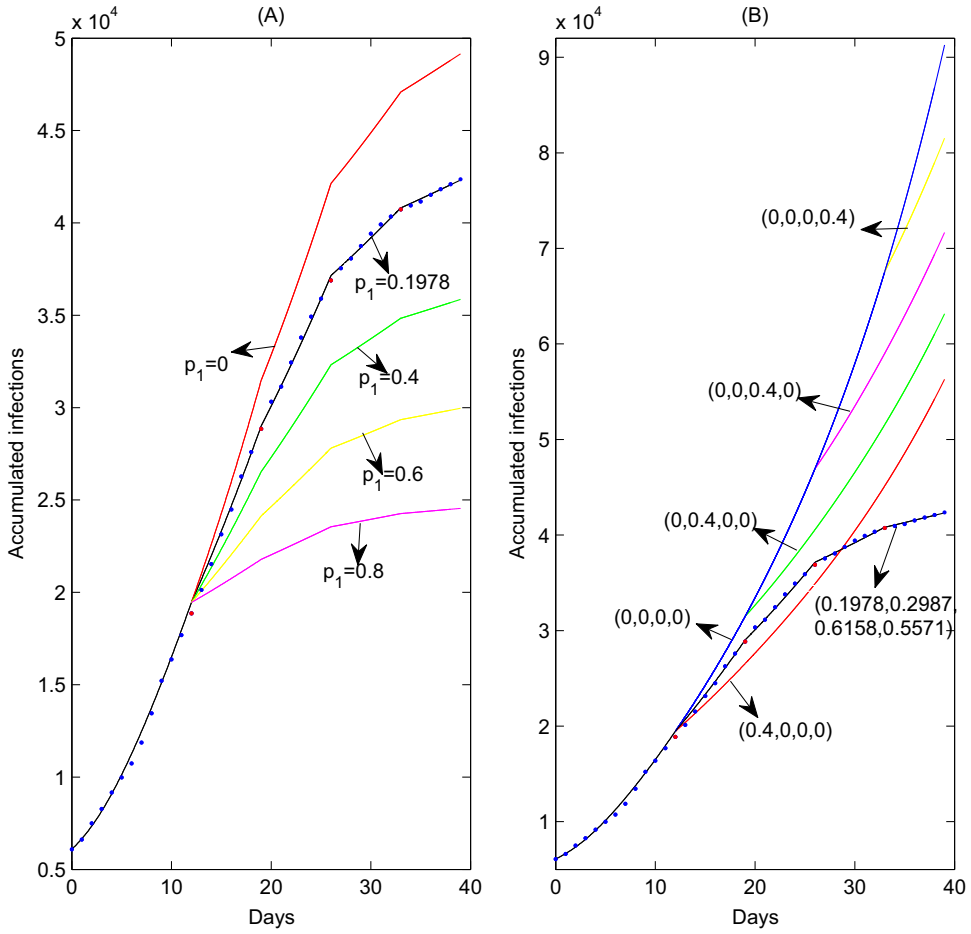

Fig. 8. The effectiveness analysis with different choices of the implementations of killing mosquitos. (A) Solutions to model (B.3) if we choose different ratios of killing mosquitos at 3 October and fixed the ratios of killing mosquitos as the estimated values at the other three times; (B) solutions to model (B.3) when just one time of killing mosquitos is carried out with a fixed ratio being chosen.

implementation of the vector-control measure with more intensity is better in terms of reducing the size of accumulated infections.

4. Conclusions and discussions

Our main focus is to inform the effectiveness of an integrated intervention program including treatment and isolation of patients, and impulsive vector-control strategies implemented on every Friday afternoon. We developed a mathematical model to closely mimic the integrated program of impulsive vector-control and continuous patient treatment and isolation implemented in the Guangdong Province of China during its 2014 dengue outbreak. We also fitted data to the model and used this model to carry out a retrospective analysis to estimate the control parameters and the control reproduction number, and to simulate outbreak outcomes under different variations of the implemented interventions.

From the viewpoint of mathematics, both the basic and type reproduction numbers act as the threshold that governs whether the disease dies out or not. In the absence of interventions, the basic reproduction number can be calculated by using the next-generation matrix introduced in van den Driessche and Watmough (2002) and Diekmann and Heesterbeek (2000). Although the basic reproduction number fails to produce the average number of secondary infections (Li et al., 2011), we keep it for comparison of the estimated value with those in the literature in which most estimated basic reproduction numbers were obtained on the basis of statistical methods and surveillance data. By fitting our model to the accumulated data in Guangdong province, we estimated the mean basic reproduction number as 1.7425 (95% CI 1.4443–2.0408). This is in broad agreement with those obtained in studies from Brazil in 1991 (1.60–2.49) (Marques et al., 1994), Mexico in 2002 (1.1–3.3) (Chowell et al., 2007) and Mexico in 1991 (1.3) (Koopman et al., 1991), from Thailand in 1980 (4.3–5.8) (Ferguson et al., 1999), Brazil in 2000 (3.58–12.86) (Massad et al., 2001) and Brazil in 2000 (2.74–11.57) (Massad et al., 2003). Using the data of accumulated infections between September 21 and October 30, we also estimated the ratios of mosquito killing as $p_1 = 0.1978$, $p_2 = 0.2987$, $p_3 = 0.6158$, $p_4 = 0.5571$, and calculated the control reproduction number as 0.1709. This reduction of the reproduction number from 1.7425 to 0.1709 suggested that the integrated interventions were highly effective to control the dengue outbreak.

Our sensitivity analysis for the control reproduction number through the evaluation of PRCCs with respect to the control parameters suggests that the choice of the dates and killing ratios are significant to reduce the control reproduction number. We also performed simulations on the control reproduction number and the epidemic unfolding in terms of number of human infections under different variations of the control strategies implemented. We illustrated in Table 4 that skipping one Friday for mosquito killing would not result in raising the control reproduction number to the threshold value 1 but would lead to significant increase in the accumulated infections on

October 30. We also noted that a one-time vector control is not sufficient to bring down the control reproduction number to the threshold 1, and neither is a larger duration between two consequent mosquito killings. Under the assumption of the same mosquito-killing ratio applied to every Friday, our simulations (Fig. 8(B)) illustrated that the earlier the vector-control strategy is implemented, the smaller the accumulated infections at the end of the outbreak.

For a vector-control program implemented across the province, pre-defined dates of mosquito-killing exercise were chosen as Friday afternoon. Our main results indicate that quicker persistent impulsive implementation of control interventions with more intensity resulted in an effective reduction in the reproduction number and hence led to a decline in new infections.

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Appendix A. Calculation for R_0 and T_0

To calculate the reproduction number of model (1), we need to consider the following equations:

$$\begin{aligned}\frac{dI_h}{dt} &= c\beta_{mh}\frac{I_m}{N_h}S_h - (\gamma_1+\gamma_2)I_h - \mu_h I_h,\ \frac{dE_m}{dt}\\ &= c\beta_{hm}\frac{I_h}{N_h}S_m - \mu_m E_m - \sigma E_m,\ \frac{dI_m}{dt} = \sigma E_m - \mu_m I_m.\end{aligned} \tag{A.1}$$

We get

$$F = \begin{pmatrix} 0 & 0 & c\beta_{mh} \\ c\beta_{hm}\dfrac{\hat{N}_m}{N_h} & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix},\quad V = \begin{pmatrix} \gamma_1+\gamma_2+\mu_h & 0 & 0 \\ 0 & \mu_m+\sigma & 0 \\ 0 & -\sigma & \mu_m \end{pmatrix} \tag{A.2}$$

where $\hat{N}_m = \frac{\Lambda}{\mu_m}$. Therefore,

$$R_0 = \rho(FV^{-1}) = \sqrt{c^2\beta_{hm}\beta_{mh}\frac{1}{\gamma_1+\gamma_2+\mu_h}\frac{\sigma}{\mu_m+\sigma}\frac{1}{\mu_m}\frac{\hat{N}_m}{N_h}}. \tag{A.3}$$

It is worth to note that there is another threshold calculated by the alternate method introduced in the papers (Heesterbeek and Roberts, 2007; Roberts and Heesterbeek, 2003), which is the so-called type-reproduction number, denoted by T_0. Let $K = FV^{-1}$, then the type-reproduction number can be easily calculated as the following:

$$T_0 = c^2\beta_{hm}\beta_{mh}\frac{1}{\gamma_1+\gamma_2+\mu_h}\frac{\sigma}{\mu_m+\sigma}\frac{1}{\mu_m}\frac{\hat{N}_m}{N_h}.$$

Appendix B. Model simplification

Due to $N_h = S_h + I_h + H_h + R_h$ being a constant and all the equations in model (1) except the one of dR_h/dt being independent of R_h, and further considering $\frac{S_h}{N_h} \approx 1$, then we have following simple model:

$$\begin{aligned}\frac{dI_h}{dt} &= c\beta_{mh}I_m - (\gamma_1+\gamma_2)I_h - \mu_h I_h,\ \frac{dH_h}{dt} = \gamma_1 I_h - \gamma_3 H_h - \mu_h H_h,\ \frac{dS_m}{dt}\\ &= \Lambda - c\beta_{hm}\frac{I_h}{N_h}S_m - \mu_m S_m,\ \frac{dE_m}{dt}\\ &= c\beta_{hm}\frac{I_h}{N_h}S_m - \mu_m E_m - \sigma E_m,\ \frac{dI_m}{dt} = \sigma E_m - \mu_m I_m.\end{aligned} \tag{B.1}$$

Compared to other parameter values, the natural death rate of human is small enough that we can assume it is nearly equal to 0, that is $\mu_h \approx 0$. Then the model can be further simplified as the following:

$$\begin{aligned}\frac{dI_h}{dt} &= c\beta_{mh}I_m - (\gamma_1+\gamma_2)I_h,\ \frac{dH_h}{dt} = \gamma_1 I_h - \gamma_3 H_h,\ \frac{dS_m}{dt}\\ &= \Lambda - c\beta_{hm}\frac{I_h}{N_h}S_m - \mu_m S_m,\ \frac{dE_m}{dt}\\ &= c\beta_{hm}\frac{I_h}{N_h}S_m - \mu_m E_m - \sigma E_m,\ \frac{dI_m}{dt} = \sigma E_m - \mu_m I_m,\end{aligned} \tag{B.2}$$

which is the final model we have used when we estimated all the parameters and the basic reproduction number R_0.

Correspondingly, when estimating the control parameters, the impulsive model (4) can be simplified as the following:

$$\left.\begin{aligned}\frac{dI_h}{dt} &= c\beta_{mh}I_m - (\gamma_1+\gamma_2)I_h,\\ \frac{dH_h}{dt} &= \gamma_1 I_h - \gamma_3 H_h,\\ \frac{dS_m}{dt} &= \Lambda - c\beta_{hm}\frac{I_h}{N_h}S_m - \mu_m S_m,\\ \frac{dE_m}{dt} &= c\beta_{hm}\frac{I_h}{N_h}S_m - \mu_m E_m - \sigma E_m,\\ \frac{dI_m}{dt} &= \sigma E_m - \mu_m I_m,\end{aligned}\right\} t \neq \tau_n^1, \tau_n^2, \tau_n^3, \tau_n^4,\ \left.\begin{aligned} S_m((4n+i-1)T^+) &= (1-p_i)S_m((4n+i-1)T),\\ E_m((4n+i-1)T^+) &= (1-p_i)E_m((4n+i-1)T),\\ I_m((4n+i-1)T^+) &= (1-p_i)I_m((4n+i-1)T),\end{aligned}\right\} t = \tau_n^i,\quad i = 1, 2, 3, 4. \tag{B.3}$$

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